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| <b>(54) Title:</b> CALIBRATION TRANSFER STANDARDS AND METHODS<br><br><b>(57) Abstract</b><br><br>The present invention provides methods of using a series of transfer standards based on designed mixtures of Rare Earth Oxides (REOs) for transferring a set of spectra from a master instrument to a slave instrument. The REOs can be in solid form or dissolved in solution or doped into a glass matrix. The transferred calibration set of spectra allows quantitative modeling for the prediction of property and/or constituent values of unknown samples. The method of the present invention applies to a variety of spectroscopic instrumental techniques including, but not limited to, near infrared, mid-infrared, Raman, ultraviolet, visible, and the like. Another feature of the present invention provides for a kit for transferring calibration measurements between spectrophotometric instruments comprising a plurality of compositions of REOs comprising one or more rare earth oxides selected from the group consisting of stable rare earth oxides. |           |  |

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## CALIBRATION TRANSFER STANDARDS AND METHODS

### Background Art

Near Infrared (NIR) spectroscopy has found increasing application in the pharmaceutical, as well as other process industries. As part of the development of a process NIR application, feasibility calibrations are often performed in a laboratory setting using research grade instrumentation prior to implementation in a process environment. In addition to the convenience of calibrating in the laboratory, research grade instruments are often more flexible and have better signal-to-noise characteristics than their process counterparts, resulting in more robust calibrations. Unfortunately, transferring multivariate calibrations between identical research instruments has proven to be problematic if not impossible, let alone between laboratory and process instruments. Accordingly, a great deal of emphasis has been placed on developing mathematical methods to compensate for differences between spectrophotometers. Most approaches have focused on the use of calibration sample subsets as a basis for transfer. Alternatively, standard agricultural samples such as grain, forage, or soybeans, and the like, have been suggested for transferring calibrations of like materials.

Unfortunately, transfer subsets or samples of like materials are unlikely to include sufficient variance to map out instrument responses over a wide dynamic range. In addition, these approaches assume: (1) that the "standard" materials are available in sufficient quantities to adequately account for lot-to-lot variability and, in some cases, (2) that the materials are chemically and physically stable for long periods of time. Neither of the assumptions is likely to hold in many cases. For example, when the product is a complex, synthetic organic molecule, stability over extended periods of time may limit the number of suitable samples available and is likely to preclude the use of a standard transfer set.

An additional potential problem with the traditional approaches to calibration transfer is that they rely on prediction error as the sole figure of merit for gauging success of a transfer. A recent article by representatives of the United States Food and Drug Administration (FDA) discusses an interest in establishing tolerances for products and processes based on a scientific signature or "fingerprint".

### Summary of the Invention

To address the issues outlined above, a series of transfer standards have been developed based on designed mixtures of the Rare Earth Oxides (REO) of holmium, erbium, and dysprosium, although other rare earth oxides can be used. The present invention, therefore, describes compositions of rare earth oxides and a method that utilizes designed mixtures of REOs together with a small number (subset) of calibration samples, ranging from 5 to 15 (although fewer or more calibration samples could be used), as a basis set for transferring a set of spectra. The subset of samples is a reduced number of samples selected from the plurality of calibration samples. The subset of samples may or may not be selected systematically. In fact, if the calibration samples are unstable, the subset may just be the best and latest few samples produced or obtained. In addition, standards of other materials which are stable for more than one month, such as elemental, inorganic or organic substances, could be added to the standard set of REOs if deemed appropriate. This transferred calibration set of spectra allows quantitative modeling for the prediction of properties or constituents, such as loss on drying (LOD), of an  $n$  number of  $\alpha$ -samples, where  $n$  is 1 to infinity.  $\alpha$ -samples are those samples (e.g., Avicel®, which is a commonly used tablet diluent and disintegrant) whose constituent and/or property values (e.g., LOD) are unknown and one would like to predict by spectroscopic calibration without running a time consuming laboratory method, such as actual laboratory measurement of LOD. In addition to constituent prediction of bulk materials and complex mixtures (e.g., LOD of Avicel®) this method is applicable to a whole host of instrumental calibrations. For example: prediction of reaction endpoints, impurity profiles, product quality and identity, sample homogeneity (uniformity), sample conformity, and the like. Further, the method of the present invention applies not only to near-infrared calibrations but also to a variety of instrumental techniques including, but not limited to, mid-infrared, Raman, ultra-violet, visible, and the like. In addition to ensuring that prediction errors are within the laboratory instrument accuracy, the method also successfully transfers the product "fingerprint".

The mathematical method and calibration standards described herein provide not only a means for transferring calibrations, but will also allow users to track the long term stability and performance of NIR spectrophotometers. As the design includes the N.I.S.T. standard wavelength reference material, a path to traceability is provided to

ensure instruments are operating within specified limits. In addition, the method can be used to correct for differences occurring as a result of instrument repair, lamp changes, and the like.

#### Detailed Description of the Invention

5 In order to adequately describe and correct for changes in instrument response, a set of generic standards are made. To construct such a set of standards, several instrumental operating range criteria need to be met: (1) the materials should be stable, preferably for more than one month; (2) they should have spectral features throughout the operating range of the instruments selected; and (3) the standards need  
10 to span a wide dynamic range of instrument response. One set of materials that meet these criteria are the oxides of rare earth metals (REO); preferably the oxides of holmium, erbium, and dysprosium. These materials are stable to 800 °C. In addition, the REOs have well defined, strongly absorbing NIR bands. It is also important to note that, taken individually, each REO has wide areas where there is no appreciable  
15 spectral response. Thus, when designed mixtures, that is mixtures which are specifically formulated to give spectral response and/or non-response in certain areas of the spectrum being scanned, are used, as described hereinbelow, the resulting standards span a wide dynamic range of response throughout the spectral region, such as the 1100 to 2100 nm spectral region of NIR. The rare earth oxides can be in solid  
20 form or dissolved in solution or doped into a glass matrix. Solid and solution compositions of REOs are formed by either acquiring them from commercial sources and/or by mixing individual REO components until the REO composition becomes homogeneous as determined by analytical methods such as spectrophotometric methods. Solutions of REOs are readily available from commercial sources such as  
25 Sigma Chemical Co., P.O. Box 14508, St. Louis, MO 63178. REO compositions doped into a glass matrix can be purchased from commercial sources such as Corion, Inc., 73 Jeffrey Ave., Holliston, MA 07146. While the standards described herein are comprised of REOs, in general standards can comprise any acceptable reference material meeting criteria 1-3 above. While it is preferable to use REOs, certain  
30 agricultural products, such as wheat, rice, and the like, or other elements or organic or inorganic materials can be suitably employed.

The REO composition can be made-up of as many REOs selected from those REOs meeting criteria 1-3 above as the user may desire and each REO component of

a mixture may range from 0 to 100% in the composition. In addition, standards of other materials, such as described above could be added to the set of REO standards, if deemed appropriate.

The spectra of a plurality of calibration samples and a plurality of subset  
5 samples are collected on the master instrument to yield a master set of calibration spectral data and subset spectral data and the spectral data of a plurality of subset samples are collected on the slave instrument to yield a slave set of subset spectral data. A master instrument can be any instrument from which one would like to transfer a calibration. Likewise, a slave instrument can be any instrument one might like to  
10 receive and operate a transferred calibration. Master and slave instruments may or may not be of the same model or type or even of the same manufacturer. It is also possible that one instrument can serve as both the master and slave where the difference between its designation arises from a change in instrument configuration. For example, it is possible to collect spectra of samples in a sample cup and it is also possible to  
15 collect spectra with a fiber optic probe attachment on the same instrument. In this case, one of the configurations would be designated as the master and the other configuration would be designated as the slave. It is further possible to designate master and slave functionality to a process which changes over time, and where the process is monitored with one instrument. In this case the plurality of calibration  
20 spectra collected at an earlier time point could be transferred to a more current time frame in order to reflect the current status of the process. In such cases, it is implied and understood that the master and slave instrument designations refer to the time domain. Calibration samples are those samples whose spectral data are measured on the master instrument and are used to establish a set of spectral data that reflect a  
25 known single or multiple constituent and/or property value.

Spectral data of all the types of samples, including the calibration samples, subset samples, standards and  $\alpha$ -samples, are collected using a suitable computer program which is commercially available and known to those skilled in the art, such as the software package Near-Infrared Spectral Analysis Software® (NSAS) version 3.27  
30 (NIRSystems Inc., Silver Springs, MD) according to manufacturer's instructions. NSAS files are translated into flat ASCII format using a suitable computer program which is commercially available and known to those skilled in the art, such as Masterkey® (Infometrix Inc., Seattle, WA) according to manufacturer's instructions. All calculations

are performed using an appropriate computer software package which is commercially available and well known to those skilled in the art, such as Matlab® for Windows® version 4.2 (The Mathworks Inc., South Natick, MA). Instrument standardization routines including direct standardization with additive baseline correction are obtained  
5 in their original form from the PLS Toolbox for Matlab®, version 1.4 (Eigenvector Technologies, Richland, WA).

The spectral data of the calibration samples are collected on the master instrument and the spectral data of the subset samples are collected on both the master and slave instruments. Care is taken to ensure that the samples with the  
10 maximum and minimum constituent and/or property and/or spectral values being measured are included in the calibration set. No preprocessing is performed prior to analysis. However, preprocessing (e.g., derivatives, multiplicative scatter corrections, standard normal variate, smoothing, detrending, etc.) can be performed if deemed appropriate for the application. Principal Component Regression (PCR) (Naes, T.,  
15 Martens, H., *J. Chemo.*, 2, pp. 155-167, 1988) is performed on the master calibration set of spectral data and used to predict the master subset. In addition to PCR, many other linear or non-linear chemometric calibration techniques can be used (e.g., multiple linear regression, simple linear regression, partial least squares, neural networks, multiple adaptive regression splines, ridge regression, continuum regression, locally  
20 weighted regression, etc.). The appropriate number of principal components (PC) to include in the model is determined with the aid of a statistic such as the Root Mean Squared Error of Prediction (RMSEP) (Naes, T., Isaksson, T., *NIR News*, 2(4), p. 16, 1991). To determine how well the "fingerprint" of the calibration set matches that of the subset, a Soft Independent Modeling by Class Analogy (SIMCA) (Wold, S., *Pattern  
25 Recognition*, 8, pp. 127-139, 1976) analysis can be performed. A Principal Component Analysis (PCA) decomposition is performed on the calibration set of spectra, and the appropriate number of Principal Components is determined by, for example, taking into consideration the amount of variability accounted for and the level of noise in the data. Once the number of Principal Components has been established the subset samples  
30 are then projected into the space defined by the selected number of Principal Components and their similarity evaluated.

When comparing an unknown sample ( $\alpha$ -sample) to a SIMCA model, there are two common approaches (or statistics) for determining goodness of fit or spectral

similarity: in-model error, and out-of-model error. The in-model-error is often termed the Mahalanobis distance (M-Dist), and is a measure of how far a sample ( $\alpha$ -sample) falls from the center of mass of the cluster formed by the calibration samples. The M-Dist is normally expressed in units of standard deviation and is calculated for the

5 number of dimensions used in the original SIMCA model. A sample with an M-Dist of five (5) resides  $5\sigma$  from the center of mass of a multi-dimensional cluster. The out-of-model error is incorporated in the residual ratio (RR) statistic, and is a measure of how much information is missed by reducing the system to the desired number of dimensions. To calculate the RR, an  $\alpha$ -sample spectrum is projected into the multi-

10 dimensional space defined by the selected number of PCs of the calibration set of spectral data, and then reconstructed by back-multiplying the resulting  $\alpha$ -sample spectrum scores times calibration set loadings. The original and reconstructed spectra are then subtracted to determine the residual error for each sample. Each sample's residual error is then divided by the average residual error of the calibration set. Thus,

15 the RR provides a relative measure of, on average, how much of the  $\alpha$ -sample's information is missed compared to the samples in the calibration set. To obtain a single statistic that indicates spectral similarity, the M-Dist and the RR are multiplied together. Thus, the resulting product provides a relative means of determining the similarity of an  $\alpha$ -sample to a calibration set, or how well the "fingerprint" of an  $\alpha$ -sample

20 matches that of a calibration set. The statistics are fully described by P.K. Aldridge et al. in *Appl. Spec.*, 48 (10), pp. 1272-1276, 1994, and by Mark, H. in *Anal. Chem.*, 58, p. 379, 1986. Determinations should not be made based on small differences in the magnitude of M-Dist\*RR values, rather more emphasis should be placed on trends in the comparison of the values between sets. An Upper Control Limit (UCL) is the

25 maximum M-Dist\*RR value for the samples in the calibration set. Thus,  $\alpha$ -samples whose M-Dist\*RR values are large compared to the UCL have a "fingerprint" that is significantly different from the calibration set. While a few samples are slightly above the UCL, in general the signatures of the calibration and subset samples are well matched.

30 To reduce the prediction error encountered when transferring an uncorrected calibration model from the master to the slave instrument (or from slave to master instrument), direct standardization is performed using spectra of subset samples and REO standards collected on both master and slave instruments as described fully by



Y. Wang et al. in *Anal. Chem.*, 63, pp. 2750-2756, 1991. In addition to direct standardization, other calibration transfer algorithms can be used. These approaches can be multivariate (e.g., piecewise direct standardization) or univariate (e.g., method of Shenk and Westerhaus, U.S. Patent No. 4,866,644). A direct standardization transfer  
5 function is obtained. The transfer function is then multiplied by the set of calibration sample spectra collected on the master instrument which makes the set of calibration sample spectra appear as though their spectra were collected on the slave instrument. The transferred calibration set is then used to construct a calibration model to predict constituent and/or property values in the subset or  $\alpha$ -sample set scanned using the  
10 slave instrument. Alternatively, the transfer set can be used to transfer the spectra from slave to the master instrument so as to allow use of the original (master) calibration model.

The direct standardization procedure is then carried out using the spectra of a mixture of REO standards, usually ten, and selected subset samples, collected on both  
15 the master and slave instruments. PCR or other selected technique is performed using the reconstructed (transferred) spectra for calibration, and the subset (slave instrument) for prediction using the constructed model.

The REO standards described herein can also provide users a basis for tracking the long term stability and performance of NIR spectrophotometers. As the designed  
20 standards can include the N.I.S.T. standard wavelength reference material, a path to traceability is provided to ensure instruments are operating within specified limits. In addition, the standards and methods of this invention can be used to compensate for differences occurring as a result of instrument repairs, lamp changes, and the like.

In addition to the method described hereinabove, the spectral data and the  
25 mathematical operations on said spectral data can be combined in further methods described hereinbelow to give the desired unknown constituent and/or property values.

Each of the methods described below require the measuring and use of certain sets of spectral data of the types of samples described hereinabove, including:  
30 measuring the spectra of each of the plurality of calibration samples on the master and/or slave spectrophotometer to obtain a set of master and/or slave calibration spectral data, respectively; measuring the spectra of each of the plurality of standards on said master and/or slave spectrophotometer to obtain a set of master and/or slave standard spectral data, respectively; measuring the spectra of each of the plurality of

subset samples on said master and/or slave spectrophotometer to obtain a set of master and/or slave subset spectral data; and measuring the spectra of  $n$   $\alpha$ -samples on the master and/or slave spectrophotometer to obtain a master and/or slave  $n$   $\alpha$ -samples spectral data, respectively. Once the appropriate spectral data sets have been  
5 acquired, the data are operated on mathematically, according to the methods discussed hereinabove, to predict the desired constituent and/or property values of the  $n$   $\alpha$ -samples from the spectral data obtained from the appropriate master or slave instrument, according to the following methods.

Method A: i) Constructing a transfer function utilizing said set of master standard spectral data, said set of master subset spectral data, said set of slave standard  
10 spectral data and said set of slave subset spectral data; (ii) constructing a set of slave transferred calibration spectral data utilizing said set of master calibration spectral data and said transfer function; (iii) constructing a slave calibration model utilizing said set of slave transferred calibration spectral data; and (iv) predicting said properties and/or  
15 said constituents of said  $n$   $\alpha$ -samples on said slave spectrophotometer utilizing said slave calibration model and said slave  $n$   $\alpha$ -samples spectral data.

Method B: (i) Constructing a transfer function utilizing said set of master standard spectral data and said set of slave standard spectral data; (ii) constructing a set of slave transferred calibration spectral data utilizing said set of master calibration spectral data  
20 and said transfer function; (iii) constructing a slave calibration model utilizing said set of slave transferred calibration spectral data; and (iv) predicting said properties and/or said constituents of  $n$   $\alpha$ -samples on said slave spectrophotometer utilizing said slave calibration model and said slave  $n$   $\alpha$ -samples spectral data.

Method C: (i) constructing a transfer function utilizing said set of master standard spectral data, said set of master subset spectral data, said set of slave standard  
25 spectral data and said set of slave subset spectral data; (ii) constructing a master calibration model utilizing said set of master calibration spectral data; (iii) constructing a transferred master  $n$   $\alpha$ -samples spectral data utilizing said slave  $n$   $\alpha$ -sample spectral data and said transfer function; and (iv) predicting said properties and/or said  
30 constituents of  $n$   $\alpha$ -samples on said master spectrophotometer utilizing said transferred  $n$  master  $\alpha$ -samples spectral data and said master calibration model.

Method D: (i) constructing a transfer function utilizing said set of master standard spectral data and said set of slave standard spectral data; (ii) constructing a master

calibration model utilizing said set of master calibration spectral data; (iii) constructing a transferred master  $n$   $\alpha$ -samples spectral data utilizing said transfer function and the slave  $n$   $\alpha$ -samples spectral data; and (iv) predicting said properties and/or said constituents of  $n$   $\alpha$ -samples on said master spectrophotometer utilizing said transferred  
5 master  $n$   $\alpha$ -samples spectral data and said master calibration model.

The present invention further provides a method of using a composition consisting of one or more rare earth oxides as calibration transfer standards for spectrophotometric instruments wherein said rare earth oxides are selected from the group consisting of stable rare earth oxides. A preferred method of the present  
10 invention utilizes a composition of rare earth oxides wherein the content of REOs in said composition consists of 100% holmium oxide, 100% erbium oxide, 100% dysprosium oxide or a combination of any two or three rare earth oxides selected from the group consisting of holmium oxide, erbium oxide and dysprosium oxide amounting to 100% of said composition. A preferred method of the present invention utilizes said  
15 composition of rare earth oxides wherein said rare earth oxides are in solid form. Another preferred method of the present invention utilizes said composition of rare earth oxides wherein said rare earth oxides are in solution. A yet another preferred method of this invention utilizes said composition of rare earth oxides wherein said rare earth oxides are doped into a glass matrix.

20 Another feature of the present invention provides for a kit for transferring calibration measurements between spectrophotometric instruments comprising a plurality of compositions of rare earth oxides comprising one or more rare earth oxides selected from the group consisting of stable rare earth oxides. The solid form of the REOs and solution of REOs can be held in any type of container. Preferably, the solid  
25 form of the REOs and solution of REOs are held in a resealable container having a pellucid window at one end of the container. The solid form of the REOs composition is preferred. A kit is defined as a collection of REO compositions. The kit can consist of only one form of REO composition (i.e., solid, solution or glass matrix) or the kit can consist of a combination of forms of REO compositions as listed above. A preferred  
30 kit of the present invention comprises compositions of rare earth oxides wherein the content of REOs in said composition is 100% holmium oxide, 100% erbium oxide, 100% dysprosium oxide or a combination of any two or three rare earth oxides selected from the group consisting of holmium oxide, erbium oxide and dysprosium oxide amounting

-10-

to 100% of the REO content in said composition. A more preferred kit of the present invention comprises a spectral baseline reference material in addition to the plurality of compositions of rare earth oxides.

The following example illustrates a method of the instant invention. The invention, however, is not limited to the example shown.

#### EXAMPLE

Ninety-one (91) samples of U.S. Pharmacopia (USP) Avicel®, grades PH101, PH102, and PH105, (*Handbook of Pharmaceutical Excipients*, Amer. Pharm. Assoc., Washington, DC, pp. 53-55, 1986) were obtained from FMC Corporation (Newark, DE) and were used as application samples. Loss on Drying (LOD), a constituent of a sample, was determined for each calibration sample following the USP method consisting of placing approximately 0.3 to 0.5 g of a calibration sample at 105 °C for 3 hours and calculating the weight loss over this period (*United States Pharmacopia & National Formulary*, USP Convention Inc., Rockville, MD, pp. 1249 & 1546, 1985). The result of LOD measurements were expressed as a percentage of the initial sample weight, % LOD. To extend the range of LOD values, 50 of the calibration samples were subjected to various humidity environments. These LOD conditions were achieved by oven drying the calibration samples or by placing them in sealed chambers (desiccators) over differing materials which modulated the relative humidities, as shown in Table 1.

Table I  
Materials for Modulation of Relative Humidity

| % Relative Humidity | Material   |
|---------------------|--|
| 0                   | P <sub>2</sub> O <sub>5</sub>  |
| 10                  | Drierite   |
| 75                  | Saturated NaCl in H <sub>2</sub> O   |
| 85                  | Saturated KCl in H <sub>2</sub> O  |
| 93                  | Saturated NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> in H <sub>2</sub> O |
| 98                  | Saturated Pb(NO <sub>3</sub> ) <sub>2</sub> in H <sub>2</sub> O              |

The spectra of the original ninety-one (91) calibration samples were combined with those of fifty (50) water challenged calibration samples for a total of one hundred forty-

one (141) spectra. Immediately prior to the determination of LOD, the sample reflectance spectra were obtained using two (2) different NIR spectrophotometers: a 6500 (designated as 'master' instrument) and a Process 5000 (designated 'slave'), both of which were obtained from NIRSystems Inc., Silver Springs, MD. Each spectrum was the average of 64 scans and encompassed the spectral range from 1100 to 2500 nm. The data interval was one point every two nanometers for a total of 700 data points per spectrum.

The master instrument was configured with a 4 inch Quant® probe (available from NIRSystems Inc., Silver Springs, MD) at the end of a 1 meter coaxial fiber optic bundle. This configuration contained 420 fibers from source to sample and 720 fibers from sample to detector (420/720). For the master instrument, the reference scan was collected against a 99% reflective Spectralon® standard (SRS-99-020, Labsphere Inc., North Sutton, NH). As the reference scan was collected via the same optical path as the sample spectra, spectral contributions due to the fiber optic were eliminated.

The slave instrument was configured with a 12 inch interactance/reflectance probe at the end of a 3 meter limited fiber optic bundle. This configuration contained 210 fibers from source to sample and 210 fibers from sample to detector (210/210). In the slave instrument case, the reference scan was collected through a shunt fiber bundle approximately 1/4 meter in length. While this configuration eliminates the need for removing the fiber optic probe from the process/sample in order to collect a reference spectrum, it also adds significant spectral features due to the uncorrected length of the fiber optic. In addition, the manufacturer recommends adding a thin film of index matching oil (Resolve, High Viscosity, Stephens Scientific, Riverdale, NJ) to the coupling where the fiber optic is terminated into the collection optics. This oil is a hydrocarbon based material whose presence adds additional features to the sample spectra.

Supplies of 99.99% pure REOs of holmium ( $\text{Ho}_2\text{O}_3$ ), dysprosium ( $\text{Dy}_2\text{O}_3$ ) and erbium ( $\text{Er}_2\text{O}_3$ ) were obtained from GFS Chemical, Columbus, Ohio. The mixtures of the REOs used in the experiment were made according to the compositions shown in Table 2. The composition of the National Institutes of Standards and Technology's (N.I.S.T.) NIR reflectance wavelength standard (SRM# 1920: 1/3 holmium, 1/3 erbium, 1/3 dysprosium) constitutes the center point of our ten (10) point simplex lattice design.

**Table 2**  
**Composition of Rare Earth Standards**

| Standard | Ho <sub>2</sub> O <sub>3</sub> | Dy <sub>2</sub> O <sub>3</sub> | Er <sub>2</sub> O <sub>3</sub> |
|----------|--------------------------------|--------------------------------|--------------------------------|
| 1        | 1                              | 0                              | 0                              |
| 2        | 1/2                            | 0                              | 1/2                            |
| 3        | 0                              | 1                              | 0                              |
| 4        | 1/2                            | 1/2                            | 0                              |
| 5        | 2/3                            | 1/6                            | 1/6                            |
| 6        | 1/3                            | 1/3                            | 1/3                            |
| 7        | 1/6                            | 1/6                            | 2/3                            |
| 8        | 1/6                            | 2/3                            | 1/6                            |
| 9        | 0                              | 1/2                            | 1/2                            |
| 10       | 0                              | 0                              | 1                              |

- 15 The total mass of each standard mixture was 12 grams with the mass of each component weighed out to  $\pm 2$  mg. For example, standard #8 was made from 2.000 g Ho<sub>2</sub>O<sub>3</sub>, 8.000 g Dy<sub>2</sub>O<sub>3</sub>, and 2.000 g Er<sub>2</sub>O<sub>3</sub>, corresponding to the 1/6, 2/3, and 1/6 fractions, respectively. The components of each mixture were weighed into a vial such as a 4 dram shell vial, loaded into a rotary mixer (Lab Quake, Labindustries Inc., Berkeley, CA) and rotated for approximately four (4) hours or until the mixture was deemed to be homogeneous, as determined by any appropriate method such as, spectroscopic analysis. After mixing, each standard was transferred into a Cam-Lock® sample cup (coarse), available from InfraSoft Inc., State College, PA, which has a window at the front end. The Cam-Lock® cups provided a convenient means for permanently sealing the REO standards as they are manufactured from heavy gauge aluminum with an O-ring seal to prevent ingress of moisture or other contaminants and are fitted with an IR grade quartz window. After placing the standards in the Cam-Lock® cups, the cups were further sealed with a spot of epoxy to prevent accidental opening.
- 20 Spectral data of all types of samples, including the calibration samples, subset samples, standards and  $\alpha$ -samples, were collected using the software package Near-Infrared Spectral Analysis Software® (NSAS) version 3.27 according to manufacturer's

instructions. NSAS files were translated into flat ASCII format using Masterkey® according to manufacturer's instructions. All calculations were performed using Matlab® for Windows® version 4.2. Instrument standardization routines including direct standardization with additive baseline correction were obtained in their original form  
5 from the PLS Toolbox for Matlab®, version 1.4.

The selected spectral range was 1100 to 2100 nm due to attenuation of the slave instrument's fiber optic in the region above 2100 nm. This subset of wavelengths was used for all subsequent calculations. The observed baseline offsets within each instrument are consistent with the varying particle size distributions and morphologies  
10 of the three grades of Avicel® used in this study. The one hundred forty-one (141) sample spectra collected on both the master and slave instruments were randomly divided into master and slave calibration spectral data sets and master and slave subset spectral data sets containing 85 and 56 samples, respectively. Care was taken to ensure that the samples with the maximum and minimum values of LOD were  
15 included in the calibration set. No preprocessing was performed prior to analysis. Principal Component Regression (PCR) was performed on the master calibration set of spectral data and used to predict the master subset. A two (2) principal component (PC) model was selected as it provided the minimum Root Mean Squared Error of Prediction (RMSEP). A linear regression of the actual LOD values versus the NIR  
20 predicted values of the subset samples using the 2 PC model showed an RMSEP value of 0.62 % LOD with a correlation coefficient,  $R^2$ , of 0.89. As expected, the uncertainty in this prediction is limited by that of the reference LOD method, estimated at 0.7% LOD. To investigate how well the "fingerprint" of the calibration set matched that of the subset, a Soft Independent Modeling by Class Analogy (SIMCA) analysis was  
25 performed. A Principal Component Analysis (PCA) decomposition was performed on the calibration set, and the subset samples were then projected into the space defined by the first four (4) PC's. All subsequent SIMCA calculations use the first four (4) PC's.

To reduce the prediction error encountered when transferring an uncorrected calibration model from the master to the slave instrument, direct standardization was  
30 performed using spectra of subset samples and REO standards collected on both master and slave instruments. A direct standardization transfer function was obtained. The transfer function was then multiplied by the set of calibration sample spectra collected on the master instrument which makes the set of calibration sample spectra

-14-

appear as though their spectra were collected on the slave instrument. The transferred calibration set was then used to construct a calibration model to predict LOD in the subset and/or  $\alpha$ -sample set scanned using the slave instrument.

- The direct standardization procedure was then carried-out using the spectra of
- 5 fifteen (15) samples: selected 5 Avicel® (subset samples) samples plus the 10 REO standards collected on both the master and slave instruments. PCA was performed using the reconstructed (transferred) spectra for calibration, and the test set (slave instrument) for prediction. The RMSEP was once again at a minimum with a two (2) PC
- 10 model for prediction of LOD with an error approximately equal to 0.60 % LOD, equivalent to the one instrument case. Results of the SIMCA modeling for the master-to-slave instrument case showed that the error in matching the "fingerprint" of the two methods are approximately equivalent.



CLAIMS

1. A method of using a composition consisting of one or more rare earth oxides as calibration transfer standards for spectrophotometric instruments wherein said rare earth oxides are selected from the group consisting of stable rare earth oxides.
- 5 2. A method according to claim 1 wherein said composition of rare earth oxides is 100% holmium oxide, 100% erbium oxide, 100% dysprosium oxide or a combination of any two or three rare earth oxides selected from the group consisting of holmium oxide, erbium oxide and dysprosium oxide, amounting to 100% of said composition.
- 10 3. A method according to claim 1 wherein said rare earth oxides are in solid form.
4. A method according to claim 1 wherein said rare earth oxides are in solution.
5. A method according to claim 1 wherein said rare earth oxides are doped  
15 into a glass matrix.
6. A kit for transferring calibration measurements between spectrophotometric instruments comprising a plurality of compositions of rare earth oxides comprising one or more rare earth oxides selected from the group consisting of stable rare earth oxides.
- 20 7. A kit according to claim 6 wherein the form of each of said plurality of compositions of rare earth oxides in said kit is each independently selected from the group consisting of the solid form, in solution and doped in a glass matrix.
8. A kit according to claim 7 wherein the content of rare earth oxides in said composition of rare earth oxides is 100% holmium oxide, 100% erbium oxide, 100%  
25 dysprosium oxide or a combination of any two or three of holmium oxide, erbium oxide and dysprosium oxide amounting to 100% of the rare earth oxides content in said composition.
9. A kit according to claim 8 which further comprises a baseline reference material.
- 30 10. A method for determining one or more properties and/or one or more constituents of an  $\alpha$ -sample on a slave spectrophotometer, comprising the steps of:

-16-

- (i) providing a plurality of subset samples, a plurality of standards, a plurality of calibration samples,  $n$   $\sigma$ -samples wherein  $n$  is an integer from 1 to infinity, a master spectrophotometer and a slave spectrophotometer;
  - (ii) measuring the spectra of each of the plurality of calibration samples on the master spectrophotometer to obtain a set of master calibration spectral data;
  - 5 (iii) measuring the spectra of each of the plurality of standards on said master spectrophotometer to obtain a set of master standard spectral data;
  - (iv) measuring the spectra of each of the plurality of subset samples on said master spectrophotometer to obtain a set of master subset spectral data;
  - 10 (v) measuring the spectra of each of the plurality of standards on the slave spectrophotometer to obtain a set of slave standard spectral data;
  - (vi) measuring the spectra of each of the plurality of subset samples on said slave spectrophotometer to obtain a set of slave subset spectral data;
  - (vii) constructing a transfer function utilizing said set of master standard spectral data, 15 said set of master subset spectral data, said set of slave standard spectral data and said set of slave subset spectral data;
  - (viii) constructing a set of slave transferred calibration spectral data utilizing said set of master calibration spectral data and said transfer function;
  - (ix) constructing a slave calibration model utilizing said set of slave transferred 20 calibration spectral data;
  - (x) measuring the spectra of  $n$   $\sigma$ -samples on the slave spectrophotometer to obtain slave  $n$   $\sigma$ -samples spectral data; and
  - (xi) predicting said properties and/or said constituents of said  $n$   $\sigma$ -samples utilizing said slave calibration model and said slave  $n$   $\sigma$ -samples spectral data.
- 25 11. A method for determining one or more properties and/or one or more constituents of an  $\sigma$ -sample on a slave spectrophotometer, comprising the steps of:
- (i) providing a plurality of standards, a plurality of calibration samples,  $n$   $\sigma$ -samples wherein  $n$  is an integer from 1 to infinity, a master spectrophotometer and a slave spectrophotometer;
  - 30 (ii) measuring the spectra of each of the plurality of calibration samples on the master spectrophotometer to obtain a set of master calibration spectral data;
  - (iii) measuring the spectra of each of the plurality of standards on said master spectrophotometer to obtain a set of master standard spectral data;

- (iv) measuring the spectra of each of the plurality of standards on the slave spectrophotometer to obtain a set of slave standard spectral data;
- (v) constructing a transfer function utilizing said set of master standard spectral data and said set of slave standard spectral data;
- 5 (vi) constructing a set of slave transferred calibration spectral data utilizing said set of master calibration spectral data and said transfer function;
- (vii) constructing a slave calibration model utilizing said set of slave transferred calibration spectral data;
- (viii) measuring the spectra of  $n$   $\alpha$ -samples on the slave spectrophotometer to obtain
- 10 slave  $n$   $\alpha$ -samples spectral data; and
- (ix) predicting said properties and/or said constituents of  $n$   $\alpha$ -samples utilizing said slave calibration model and said slave  $n$   $\alpha$ -samples spectral data.

12. A method for determining one or more properties and/or one or more constituents of an  $\alpha$ -sample on a master spectrophotometer, comprising the steps of:
- 15 (i) providing a plurality of subset samples, a plurality of standards, a plurality of calibration samples,  $n$   $\alpha$ -samples wherein  $n$  is an integer from 1 to infinity, a master spectrophotometer and a slave spectrophotometer;
  - (ii) measuring the spectra of each of the plurality of calibration samples on the master spectrophotometer to obtain a set of master calibration spectral data;
  - 20 (iii) measuring the spectra of each of the plurality of standards on said master spectrophotometer to obtain a set of master standard spectral data;
  - (iv) measuring the spectra of each of the plurality of subset samples on said master spectrophotometer to obtain a set of master subset spectral data;
  - (v) measuring the spectra of each of the plurality of standards on the slave
  - 25 spectrophotometer to obtain a set of slave standard spectral data;
  - (vi) measuring the spectra of each of the plurality of subset samples on said slave spectrophotometer to obtain a set of slave subset spectral data;
  - (vii) measuring the spectra of  $n$   $\alpha$ -samples on the slave spectrophotometer to obtain a slave  $n$   $\alpha$ -samples spectral data;
  - 30 (viii) constructing a transfer function utilizing said set of master standard spectral data, said set of master subset spectral data, said set of slave standard spectral data and said set of slave subset spectral data;

- (ix) constructing a master calibration model utilizing said set of master calibration spectral data;
  - (x) constructing transferred master  $n$   $\alpha$ -samples spectral data utilizing said slave  $n$   $\alpha$ -sample spectral data and said transfer function; and
  - 5 (xi) predicting said properties and/or said constituents of  $n$   $\alpha$ -samples utilizing said transferred  $n$  master  $\alpha$ -samples spectral data and said master calibration model.
13. A method for determining one or more properties and/or one or more constituents of an  $\alpha$ -sample on a master spectrophotometer, comprising the steps of:
- (i) providing a plurality of standards, a plurality of calibration samples,  $n$   $\alpha$ -samples
  - 10 wherein  $n$  is an integer from 1 to infinity, a master spectrophotometer and a slave spectrophotometer;
  - (ii) measuring the spectra of each of the plurality of calibration samples on the master spectrophotometer to obtain a set of master calibration spectral data;
  - (iii) measuring the spectra of each of the plurality of standards on said master
  - 15 spectrophotometer to obtain a set of master standard spectral data;
  - (iv) measuring the spectra of each of the plurality of standards on the slave spectrophotometer to obtain a set of slave standard spectral data;
  - (v) measuring the spectra of  $n$   $\alpha$ -samples on the slave spectrophotometer to obtain a slave  $n$   $\alpha$ -samples spectral data;
  - 20 (vi) constructing a transfer function utilizing said set of master standard spectral data and said set of slave standard spectral data;
  - (vii) constructing a master calibration model utilizing said set of master calibration spectral data;
  - (viii) constructing transferred master  $n$   $\alpha$ -samples spectral data utilizing said transfer
  - 25 function and the slave  $n$   $\alpha$ -samples spectral data; and
  - (ix) predicting said properties and/or said constituents of  $n$   $\alpha$ -samples utilizing said transferred master  $n$   $\alpha$ -samples spectral data and said master calibration model.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 95/00262

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 G01N21/27 G01N21/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | DATABASE INSPEC<br>INSTITUTE OF ELECTRICAL ENGINEERS,<br>STEVENAGE, GB<br>Inspec No. 2919728<br>WEIDNER V R ET AL 'Holmium oxide solution<br>wavelength standard from 240 to 640 nm -<br>SRM 2034'<br>see abstract<br>& JULY 1986, USA, NBS-SP-260-102 | 1,2,4,<br>6-8         |
| A          | US,A,4 836 673 (ESQUIVEL H J BENJAMIN) 6<br>June 1989<br>see column 2, line 20 - line 40; claims   | 1,2,4,<br>6-8         |
| A          | GB,A,1 346 770 (SECR DEFENCE) 13 February<br>1974<br>see page 1, line 66 - line 78; claim 1  | 1,4,6,7               |
|            | -/--   |                       |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

14 December 1995

Date of mailing of the international search report

8. 03. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 cpu nl,  
Fax (+ 31-70) 340-3016

Authorized officer

KRAMETZ E.M.

3

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/IB 95/00262

| C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
|---|---|-----------------------|
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages                            | Relevant to claim No. |
| A   | EP,A,0 098 075 (INFRARED ENG) 11 January 1984<br>see page 8, line 9 - line 30<br>see claim 9; figure 1<br>--- | 1,5-7                 |
| A   | US,A,4 461 718 (KAYE WILBUR I ET AL) 24 July 1984<br>see column 2, line 22 - line 34; claims<br>-----         | 1,4,6,7               |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 95/00262

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. CLAIMS : 1 - 9
2. CLAIMS : 10 - 13

FOR FURTHER INFORMATION PLEASE SEE FORM PCT/ISA/206 MAILED 22.12.95

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
  
1 - 9

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

information on parent family members

with                      Social Application No                     

PCT/IB 95/00262

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| US-A-4836673                              | 06-06-89            | NONE                       |                     |
| GB-A-1346770                              | 13-02-74            | NONE                       |                     |
| EP-A-0098075                              | 11-01-84            | GB-A- 2122768              | 18-01-84            |
|   |                     | JP-C- 1760465              | 20-05-93            |
|   |                     | JP-B- 4045772              | 27-07-92            |
|   |                     | JP-A- 59085946             | 18-05-84            |
|   |                     | US-A- 4465929              | 14-08-84            |
| US-A-4461718                              | 24-07-84            | NONE                       |                     |